



US008133903B2

(12) **United States Patent**
Gonzalez-Cadavid et al.

(10) **Patent No.:** **US 8,133,903 B2**
(45) **Date of Patent:** **Mar. 13, 2012**

(54) **METHODS OF USE OF INHIBITORS OF PHOSPHODIESTERASES AND MODULATORS OF NITRIC OXIDE, REACTIVE OXYGEN SPECIES, AND METALLOPROTEINASES IN THE TREATMENT OF PEYRONIE'S DISEASE, ARTERIOSCLEROSIS AND OTHER FIBROTIC DISEASES**

5,990,103 A 11/1999 Schonharting et al.
6,127,363 A * 10/2000 Doherty et al. 514/220
6,143,746 A 11/2000 Daugan et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CA 2351904 12/2001

(Continued)

OTHER PUBLICATIONS

Burdick et al, CXCL11 Attenuates Bleomycin-induced Pulmonary Fibrosis via Inhibition of Vascular Remodeling, American Journal of Respiratory and Critical Care Medicine vol. 171, pp. 261-268, printed pp. 1-5, especially page 1.*

(Continued)

Primary Examiner — Sreeni Padmanabhan

Assistant Examiner — Timothy E Betton

(74) *Attorney, Agent, or Firm* — Blakely Sokoloff Taylor & Zafman LLP

(75) Inventors: **Nestor F. Gonzalez-Cadavid**, Pasadena, CA (US); **Jacob Rajfer**, Rolling Hills Est, CA (US)

(73) Assignee: **Los Angeles Biomedical Research Institute at Harbor—UCLA Medical Center**, Torrance, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 556 days.

(21) Appl. No.: **10/779,069**

(22) Filed: **Feb. 13, 2004**

(65) Prior Publication Data

US 2005/0085486 A1 Apr. 21, 2005

(30) Foreign Application Priority Data

Oct. 21, 2003 (WO) PCT/US03/33400

(51) **Int. Cl.**
A01N 43/42 (2006.01)

(52) **U.S. Cl.** **514/310**

(58) **Field of Classification Search** 514/310
See application file for complete search history.

(56) References Cited

U.S. PATENT DOCUMENTS

5,482,039 A * 1/1996 Place 128/653.1
5,824,669 A 10/1998 Garvey et al.
5,981,563 A 11/1999 Lowrey

(57) ABSTRACT

The present methods and compositions are of use for treatment of conditions involving fibrosis, such as Peyronie's disease plaque, penile corporal fibrosis, penile veno-occlusive dysfunction, Dupuytren's disease nodules, vaginal fibrosis, clitoral fibrosis, female sexual arousal disorder, abnormal wound healing, keloid formation, general fibrosis of the kidney, bladder, prostate, skin, liver, lung, heart, intestines or any other localized or generalized fibrotic condition, vascular fibrosis, arterial intima hyperplasia, atherosclerosis, arteriosclerosis, restenosis, cardiac hypertrophy, hypertension or any condition characterized by excessive fibroblast or smooth muscle cell proliferation or deposition of collagen and extracellular matrix in the blood vessels and/or heart. In certain embodiments, the compositions may comprise a PDE-4 inhibitor, a PDE-5 inhibitor, a compound that elevates cGMP and/or PKG, a stimulator of guanylyl cyclase and/or PKG, a combination of a compound that elevates cGMP, PKG or NO with an antioxidant that decreases ROS, or a compound that increases MMP activity.

5 Claims, 21 Drawing Sheets

